

PATENT Applic. Ser. No. 09/254,617

- 64. A pharmaceutical composition comprising two adenovirus vectors, wherein each vector comprises a nucleic acid encoding a different neurotrophic factor.
- 65. (amended) The pharmaceutical composition according to claim 64, wherein the vectors comprise an expression cassette for the simultaneous expression of two different neurotrophic factors.
- 66. The pharmaceutical composition according to claim 64, wherein the neurotrophic factors are selected from GDNF, BDNF, CNTF and NT3.
- 67. (amended) The pharmaceutical composition according to claim 66, wherein the adenovirus vectors are two replication defective recombinant adenoviruses, and wherein one adenovirus comprises a nucleic acid encoding CNTF and one adenovirus comprises a nucleic acid encoding GDNF.
- 68. (amended) The pharmaceutical composition according to claim 66, wherein the adenovirus vectors are two replication defective recombinant adenoviruses, and wherein one adenovirus comprises a nucleic acid encoding GDNF and one adenovirus comprises a nucleic acid encoding NT3.
- 69. (amended) The pharmaceutical composition according to claim 66, wherein the adenovirus vectors are two replication defective recombinant adenoviruses, and wherein one adenovirus comprises a nucleic acid encoding BDNF and one adenovirus comprises a nucleic acid encoding NT3.
 - 70. The pharmaceutical composition according to claim 64, in an injectable form.
- 71. The pharmaceutical composition according to claim 64, further comprising riluzole.
 - 72. The pharmaceutical composition according to claim 71, in an injectable form.
- 73. The pharmaceutical composition of claim 64, wherein one of the neurotrophic factors is CNTF.
- 74. The pharmaceutical composition of claim 64, wherein one of the neurotrophic factors is BDNF.
- 75. (amended) The pharmaceutical composition of claim 64, wherein at least one adenovirus vector is a replication defective recombinant adenovirus vector.



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- 76. (new) A method of treating amyotrophic lateral sclerosis comprising administering to a subject by systemic administration a pharmaceutical composition comprising an adenovirus vector comprising a nucleic acid encoding a neurotrophic factor, wherein the treatment results in a reduction in progressive motor neuron degeneration in said subject.
- 77. (new) A method of treating amyotrophic lateral sclerosis comprising administering to a subject by systemic administration a pharmaceutical composition comprising an adenovirus vector comprising a nucleic acid encoding a neurotrophic factor, wherein the treatment results in a reduction in progressive denervation in said subject.
- 78. (new) The method of claim 76, wherein the reduction in progressive motor neuron degeneration is detectable by a change in the rate of loss of the number of myelinized fibers in a peripheral nervous tissue.
- 79. (new) The method of claim 77, wherein the reduction in progressive denervation is detectable by electromyography.
- 80. (new) The method of claim 76, wherein the adenovirus vector comprises an expression cassette comprising a nucleic acid encoding a neurotrophic factor under the control of a transcriptional promoter.
- 81. (new) The method of claim 77, wherein the adenovirus vector comprises an expression cassette comprising a nucleic acid encoding a neurotrophic factor under the control of a transcriptional promoter.
- 82. (new) The method of claim 78, wherein the adenovirus vector comprises an expression cassette comprising a nucleic acid encoding a neurotrophic factor under the control of a transcriptional promoter.
- 83. (new) The method of claim 79, wherein the adenovirus vector comprises an expression cassette comprising a nucleic acid encoding a neurotrophic factor under the control of a transcriptional promoter.
- 84. (new) The method of claim 76, wherein the adenovirus vector comprises two expression cassettes, wherein each cassette comprises a nucleic acid encoding a different neurotrophic factor under the control of a transcriptional promoter.



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- 85. (new) The method of claim 77, wherein the adenovirus vector comprises two expression cassettes, wherein each cassette comprises a nucleic acid encoding a different neurotrophic factor under the control of a transcriptional promoter.
- 86. (new) The method of claim 78, wherein the adenovirus vector comprises two expression cassettes, wherein each cassette comprises a nucleic acid encoding a different neurotrophic factor under the control of a transcriptional promoter.
- 87. (new) The method of claim 79, wherein the adenovirus vector comprises two expression cassettes, wherein each cassette comprises a nucleic acid encoding a different neurotrophic factor under the control of a transcriptional promoter.
- 88. (new) The method of claim 76, wherein the neurotrophic factor is GDNF, CNTF, BDNF or NT3.
- 89. (new) The method of claim 77, wherein the neurotrophic factor is GDNF, CNTF, BDNF or NT3.
- 90. (new) The method of claim 78, wherein the neurotrophic factor is GDNF, CNTF, BDNF or NT3.
- 91. (new) The method of claim 79, wherein the neurotrophic factor is GDNF, CNTF, BDNF or NT3.
- 92. (new) The method of claim 76, wherein the adenovirus vector comprises an expression cassette comprising two nucleic acid sequences, wherein each nucleic acid sequence encodes a different neurotrophic factor under the control of a single transcriptional promoter.
- 93. (new) The method of claim 92, wherein the neurotrophic factors are selected from GDNF, CNTF, BDNF and NT3.
- 94. (new) The method of claim 93, wherein the neurotrophic factors are CNTF and GDNF.
- 95. (new) The method of claim 92, wherein the transcriptional promoter is a constitutive eucaryotic or viral promoter.
- 96. (new) The method of claim 95, wherein the promoter is selected from a CMV, RSV, or adenovirus promoter.
- 97. (new) The method of claim 76, wherein the systemic administration comprises intravenous administration.



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- 98. (new) The method of claim 77, wherein the systemic administration comprises intravenous administration.
- 99. (new) The method of claim 78, wherein the systemic administration comprises intravenous administration.
- 100. (new) The method of claim 79, wherein the systemic administration comprises intravenous administration.
 - 101. (new) The method of claim 76, further comprising administering riluzole.
 - 102. (new) The method of claim 77, further comprising administering riluzole.
 - 103. (new) The method of claim 78, further comprising administering riluzole.
 - 104. (new) The method of claim 79, further comprising administering riluzole.
 - 105. (new) The method of claim 84, further comprising administering riluzole.
 - 106. (new) The method of claim 85, further comprising administering riluzole.
 - 107. (new) The method of claim 88, further comprising administering riluzole.
 - 108. (new) The method of claim 89, further comprising administering riluzole.
- 109. (new) A method of treating amyotrophic lateral sclerosis comprising administering to a subject by systemic administration a pharmaceutical composition comprising an adenovirus vector comprising a nucleic acid encoding a neurotrophic factor, wherein the treatment results in increased lifespan for said subject.
- 110. (new) The method of claim 109, wherein the adenovirus vector comprises an expression cassette comprising a nucleic acid encoding a neurotrophic factor under the control of a transcriptional promoter.
- 111. (new) The method claim 109, wherein the adenovirus vector comprises two expression cassettes, wherein each cassette comprises a nucleic acid encoding a different neurotrophic factor under the control of a transcriptional promoter.
- 112. (new) The method of claim 109, wherein the neurotrophic factor is one of GDNF, CNTF, BDNF or NT3.
- 113. (new) The method of claim 109, wherein the adenovirus vector comprises an expression cassette comprising two nucleic acid sequences, wherein each nucleic acid sequence encodes a different neurotrophic factor under the control of a single transcriptional promoter.



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- 114. (new) The method of claim 111, wherein the neurotrophic factors are selected from GDNF, CNTF, BDNF and NT3.
- 115. (new) The method of claim 111, wherein the neurotrophic factors are CNTF and GDNF.
- 116. (new) The method of claim 110, wherein the transcriptional promoter is a constitutive eucaryotic or viral promoter.
- 117. (new) The method of claim 116, wherein the promoter is selected from a CMV, RSV, or adenovirus promoter.
 - 118. (new) The method of claim 109, wherein the neurotrophic factor is CNTF.
 - 119. (new) The method of claim 109, wherein the neurotrophic factor is GDNF.
 - 120. (new) The method of claim 109, wherein the neurotrophic factor is BDTF
 - 121. (new) The method of claim 109, wherein the neurotrophic factor is NT3.
 - 122. (new) The method of claim 109, further comprising administering riluzole.
 - 123. (new) The method of claim 111, further comprising administering riluzole.
 - 124. (new) The method of claim 112, further comprising administering riluzole.
- 125. (new) The method of claim 109, wherein the systemic administration comprises intravenous administration.
- 126. (new) The method of claim 111, wherein the systemic administration comprises intravenous administration.
- 127. (new) The method of claim 112, wherein the systemic administration comprises intravenous administration.
- 128. (new) The method of claim 122, wherein the systemic administration comprises intravenous administration.